Remarks

I. Support for Amendments

The forgoing amendments to the specification are made to provide the sequence listing as required under 37 C.F.R. 1.821-1.825, and to insert the appropriate sequence identification numbers into the specification. In accordance with 37 C.F.R. § 1.821(f), the paper copy of the Sequence Listing and the computer readable copy of the Sequence Listing submitted herewith in the above-mentioned application are the same. In accordance with 37 C.F.R. § 1.821(g), this submission includes no new matter.

Support for the foregoing amendments to the claims can be found throughout the specification. Entry of the amendments and consideration of the present application are respectfully requested.

II. Status of the Claims

By the foregoing amendments, claims 1-8 and 11-14 have been amended. These amendments do not add new matter. Upon entry of the foregoing amendments, claims 1-14 are pending in the application, with claims 1, 2, 3 and 4 being the independent claims.

III. Summary of the Office Action

In the Office Action dated August 28, 2002, the Examiner has made seven rejections of the claims. Applicants respectfully offer the following remarks to overcome or traverse each of these elements of the Office Action.

IV. The Rejection Under 35 U.S.C. § 112, First Paragraph

In the Office Action at pages 2-3, the Examiner has rejected claims 4-9 and 12-14 under 35 U.S.C. § 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that the term "gene" is improperly described in the specification, because, unlike prokaryotes, the eukaryotic "gene" encompasses regions which regulate gene expression that reside both 5' and 3' to the coding regions (which regulate gene expression), and introns as well. Applicants respectfully disagree and direct the examiner to the specification at page 3, lines 2-8 and lines 12-16 which discloses that "the gene comprises DNA coding for the amino acid sequence of the protein together with associated 5′ and 3′ UTR sequences comprising appropriate expression control elements." In view of the disclosure in the specification, the term "gene" has been described clearly as encompassing regions which regulate gene expression ("appropriate expression control elements") both 5′ and 3′ to the coding regions and represents a clear and complete description of a "gene" as required under 35 U.S.C. § 112, first paragraph.

The Examiner has the burden of proving that sufficient written description of the claimed invention is not provided (MPEP § 2163). Applicants respectfully submit that in view of the description of a "gene" noted in the specification above, the skilled artisan would recognize the term "gene" to encompass regions that regulate gene expression and introns, as well as coding regions. Therefore, the specification provides a clear and complete description

the invention defined by the claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph are therefore respectfully requested.

V. The Rejection Under 35 U.S.C. § 112, Second Paragraph

In the Office Action at page 3-4, the Examiner has rejected claims 1-14 under 35 U.S.C. §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention." Applicants respectfully traverse this rejection.

A. The Rejection of Claims 1-3, 10 and 11

With regard to claims 1-3, 10 and 11, the Examiner asserts that it is unclear whether it is the DNA expression system, the mRNA, or the mRNA instability sequence that is contacted with a test compound. By the forgoing amendments, claims 1, 2 and 3 (and thus 10 and 11 that depend ultimately therefore) clearly recite that it is the DNA expression system that is contacted with a test compound.

The Examiner also states that it is unclear as to whether the DNA expression system would generate detectable signal in the presence of the test compound. Applicants note that claims 1, 2 and 3 (and thus 10 and 11 that depend ultimately therefrom) clearly recite "(b) measuring the detectable signal in the presence of the(each) test compound." Therefore, the DNA expression system would clearly generate a detectable signal in the presence of a test compound.

The Examiner also asserts that in claims 3, 10, and 11, it is unclear what features of the compound – structure, function, or nomenclature – are being compared. By the forgoing amendments, claim 3 (and therefore claims 10 and 11 that depend ultimately therefrom) clearly recites: "(c) comparing the signals obtained to determine the mRNA instability-promoting activity of the compounds." It is clearly therefore the instability-promoting activity of the compounds that is being compared.

In view of the forgoing remarks and amendments, reconsideration and withdrawal of the rejection to claims 1-3, 10 and 11 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

B. The Rejection of Claims 4-9 and 12-14

The Examiner has rejected claims 4-9 and 12-14, asserting that the word "associated" renders the claims indefinite. By the forgoing amendments, the word "associated" has been removed from claim 4 (and therefore claims 5-8 and 12-14 that depend ultimately therefrom), claim 6 (and therefore claim 14 that depends ultimately therefrom), claim 7 (and therefore claim 14 that depends ultimately therefrom) and claim 8 (and therefore claims 9, 13 and 14 that depend ultimately therefrom). The claims now recite: ". . . the gene comprises DNA coding for the amino acid sequence of the protein operably linked to 5′ and 3′ UTR sequences . . . ."

The Examiner further asserts that the recitation of "expression control elements and DNA corresponding to at least one copy of a mRNA instability sequence" is indefinite as it is unclear whether it is the "expression control elements" or the "DNA" that is "corresponding

to at least one copy of a mRNA instability sequence." By the forgoing amendments, claim 4 (and therefore claims 5-9 and 12-14 that depend ultimately therefrom) clearly indicates that it is the DNA which corresponds to at least one copy of an mRNA instability sequence.

In view of the forgoing remarks and amendments, reconsideration and withdrawal of the rejection to claims 4-9 and 12-14 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

C. The Rejection of Claims 5, 7-9, 13 and 14

The Examiner has rejected claims 5, 7-9, 13 and 14 as being indefinite as to whether the cell line is stably transfected with the reporter gene, or with some other construct wherein the cell line further comprises the reporter gene. By the forgoing amendments, claim 5 (and claims 7, 13 and 14 that ultimately depend therefrom) and claim 8 (and claims 9, 13 and 14 that ultimately depend therefrom) recite: "A stably transfected cell line comprising *the* reporter gene DNA expression system of claim 4 . . . (emphasis added)." It appears that the Examiner has interpreted "reporter gene" to be separate from "DNA expression system," when in fact, "reporter gene DNA expression system" is an inclusive system comprising a gene coding for the amino acid sequence of the protein, operably linked to 5′ and 3′ UTR sequences, which comprise appropriate expression control elements and DNA, wherein the DNA corresponds to at least one copy of a mRNA instability sequence.

In view of the forgoing remarks and amendments, reconsideration and withdrawal of the rejection to claims 5, 7-9, 13 and 14 under U.S.C. § 112 second paragraph, are respectfully requested.

D. The Rejection of Claims 1 and 2

The Examiner has rejected claims 1 and 2 as being incomplete for omitting essential steps relating to how to determine whether the compound affects mRNA stability. By the forgoing amendments, claim 1 recites: "(c) comparing the magnitude of the signal detected with a control, wherein when the magnitude of the signal detected is decreased relative to the control, said test compound destabilizes mRNA." Amended claim 2 recites: "(c) comparing the magnitude of the signal detected with a control, wherein when the signal detected is decreased relative to the control, said compound induces mRNA degradation." Applicants submit that this step clearly defines to how to determine whether the compound affects mRNA stability.

In view of the forgoing remarks and amendments, reconsideration and withdrawal of the rejection to claims 1 and 2 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

E. The Rejection of Claim 11

The Examiner has rejected claim 11 as being indefinite for merely reciting a use without any active, positive steps delimiting how this use is actually practiced. By the forgoing amendments, claim 11 recites: a method of treating or preventing a disease or medical condition in a subject, wherein the disease or medical condition is associated with inappropriate mRNA stabilisation and/or accumulation and undesirable protein expression, comprising administering to the subject the compound of claim 10. Applicants submit that this claim clearly recites positive steps delimiting how this claim is practiced. Reconsideration and

withdrawal of the rejection of claim 11 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

F. Summary

In view of the foregoing amendments and remarks, Applicants respectfully assert that claims 1-14 are not indefinite. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are respectfully requested.

VI. The Rejection of claim 11 Under 35 U.S.C. § 101

In the Office Action at pages 4-5, the Examiner has rejected claim 11 under 35 U.S.C. § 101 as being an improper process claim for failing to set forth steps involved in the process. Applicants respectfully traverse this rejection.

By the forgoing amendment to claim 11 noted above, claim 11 is now a method claim that clearly recites positive steps involved in the method. Applicants therefore submit that claim 11 is a proper process claim. Reconsideration and withdrawal of the rejection of this claim under 35 U.S.C. § 101 are respectfully requested.

VII. The Rejection Under 35 U.S.C. § 102(b) Over Banholzer

In the Office Action at pages 5-6, the Examiner has rejected claims 1-7, 10 and 12-14 under 35 U.S.C. § 102(b) as being anticipated by Banholzer *et al.* (reference AT1; hereinafter "Banholzer"). Applicants respectfully traverse this rejection.

According to the Examiner, Banholzer discloses rapamycin promoted posttranscriptional degradation of IL-3 transcripts via 3′ UTR. The Examiner also states that Banholzer discloses stably transfected cells lines containing IL-3 expression systems with or without an mRNA instability sequence. The Examiner asserts that the method and assay system disclosed by Banholzer can be used to identify compounds that induce mRNA degradation, and therefore Banholzer discloses the instant claimed invention.

Claims 1-4 of Applicants' present invention (and claims 5-7, 10 and 12-14 that depend ultimately therefrom) recite various methods for identification of compounds which affect mRNA stability, all of which rely on a common "DNA expression system . . . capable of expressing a protein having a detectable signal." The method used by Banholzer is described at page 3255, as an RNA transcription system and a cell proliferation system specifically utilizing Northern blotting and cell counting methods of quantitation. In contrast to the present invention, Banholzer does not teach the use of a DNA expression system to detect a protein signal. Hence, Banholzer does not disclose at least one element of the claimed invention.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. Since Banholzer does not expressly or inherently disclose one or more elements of the claimed invention, this reference cannot and does not anticipate claims 1-7, 10 and 12-14. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Banholzer are respectfully requested.

VIII. The Rejection Under 35 U.S.C. § 103(a) Over Danner and Maniatis

In the Office Action at pages 6-8, the Examiner has rejected claims 4, 8 and 9 under 35 U.S.C. § 103(a) as being obvious over Danner *et al.* (reference AS4; hereinafter "Danner") in view of Maniatis *et al.* (Doc. U cited on the Form PTO-892 attached to Paper No. 7; hereinafter "Maniatis"). Applicants respectfully traverse this rejection.

According to the Examiner, Danner teaches a cell line transfected with a chimeric expression vector comprising β-globulin and 3′ UTR of β2AR, with or without an mRNA instability sequence. The Examiner also states that Danner teaches that the half-life of the β-globulin/β2AR mRNA decreases upon cellular stimulation of isoproterenol or forskolin. The Examiner asserts that while Danner does not teach methods to stably transfect cells, it would have been obvious to combine the teachings of Danner with the teachings of Maniatis, who teaches a method to stably transfect cells. The Examiner concludes that the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claim 4 of Applicants' present invention (and claims 8 and 9 that depend ultimately therefrom) is directed to a reporter gene DNA expression system comprising a gene coding for expression of a protein having a detectable signal, wherein the gene comprises DNA coding for the amino acid sequence of the protein operably linked to 5′ and 3′ UTR sequences, wherein said 5′ and 3′ UTR sequences comprise appropriate expression control elements and DNA, wherein the DNA corresponds to at least one copy of a mRNA instability sequence.

In contrast, Danner teaches expression vectors and the use thereof to analyze the effect of isoproterenol and forskolin on the β_2AR mRNA instability sequence of RNA transcribed

from the vector, as measured by RNA analysis (Northern blotting). Danner does not teach that these vectors comprise a gene coding for a protein having a detectable signal. For these reasons, Danner is seriously deficient as a primary reference upon which to base an alleged *prima facie* case of obviousness of claims 4, 8 and 9. The disclosure of Maniatis does not cure these deficiencies, as Maniatis simply discloses a method of stable transfection of mammalian cells. Hence, one of ordinary skill would not have obtained the claimed invention by combining these two references.

In view of the foregoing remarks, Applicants respectfully assert that claims 4, 8 and 9 would not have been obvious over the disclosures of Danner and Maniatis, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Danner in view of Maniatis therefore are respectfully requested.

IX. Other Matters

Applicants note that the Information Disclosure Statement 1449 forms attached to the non-final Office Action dated August 28, 2002 (Paper No. 7) included pages 1-5 and 8-11 of the Applicants' original submission. However, pages 6 and 7 citing documents AR6-AT6 and AR7-AT7 were not received. Applicants respectfully request that the Examiner return copies of these pages, noting that the citations were reviewed, with the next Office Action.

X. Conclusion

All of the stated grounds of rejection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Version with markings to show changes made

In the Specification:

Two pages entitled "Sequence Listing" appended hereto which contain the sequence listings referred to in the specification have been attached to the specification.

In the specification at page 4, the paragraph appearing at lines 26-28 has been amended as follows:

As described in the above publications mRNA instability sequences often contain one or more copies of sequence motifs, e.g. selected from: AUUUA (SEQ ID NO:1); UAUUUAU (SEQ ID NO:2); UUAUUUA(U/A)(U/A) (SEQ ID NO:3), and AUUUAUUUA (SEQ ID NO:4).

In the specification at page 5, the paragraph appearing at lines 18-23 has been amended as follows:

Thus by way of illustration of the invention a preferred mRNA instability sequence for use in the identification of compounds which destabilise IL-1β mRNA is derived from the 3′ UTR of IL-1β mRNA, e.g. the sequence shown in Figure 1 (SEQ ID NO:5). More preferably the IL-1β mRNA instability sequence may comprise a fragment of the 3′ UTR of IL-1β mRNA. For example, a particularly preferred IL-1β mRNA instability sequence

comprises the 30 nucleotide sequence derived from the 3′ UTR of IL-1β mRNA (shown in Figure 2) (SEQ ID NO:6 and SEQ ID NO:7).

In the Claims:

The claims have been amended as follows:

Claims 1-8 and 11-14 have been amended as follows:

1. (Once amended) A method for the identification of a compound which affects mRNA stability, comprising:

(a) contacting a test compound with [in which] a DNA expression system which, in the absence of the test compound, is capable of expressing a protein having a detectable signal, [and] wherein [the] mRNA which codes for the protein and which is transcribed from the expression system comprises at least one copy of a mRNA instability sequence; [is contacted with a test compound and the detectable signal is measured in the presence of the test compound and compared with a control.]

(b) measuring the detectable signal in the presence of the test compound; and

(c) comparing the magnitude of the signal detected with a control, wherein when the magnitude of the signal detected is decreased relative to the control, said test compound destabilizes mRNA.

2. (Once amended) A method [according to claim 1,] for the identification of a compound which induces mRNA degradation, comprising:

(a) contacting the compound with a DNA expression system which, in the absence of the compound, is capable of expressing a protein having a detectable signal, wherein [the] mRNA which codes for the protein and which is transcribed from the expression system comprises at least one copy of a mRNA instability sequence;[,]

(b) measuring the detectable signal in the presence of the test compound; and

(c) comparing the [result obtained with a control.] magnitude of the signal detected with a control,

wherein when the signal detected is decreased relative to the control, said compound induces mRNA degradation.

3. (Once amended) A method for the comparison of compounds which induce mRNA degradation, comprising:

(a) separately contacting the compounds with a DNA expression system which in the absence of the compounds is capable of expressing a protein having a detectable signal, wherein [the] mRNA which codes for the protein and which is transcribed from the expression system comprises at least one copy of a mRNA instability sequence;[,]

(b) measuring the detectable signal in the presence of each test compound; and

(c) comparing the signals obtained to determine the mRNA instability-promoting activity of the compounds.

4. (Once amended) A reporter gene DNA expression system comprising a gene coding for expression of a protein having a detectable signal, wherein the gene comprises DNA coding for the amino acid sequence of the protein [together with associated] operably linked to 5′ and 3′ UTR sequences, wherein said 5′ and 3′ UTR sequences comprise [comprising] appropriate expression control elements and DNA, wherein the DNA codes for [corresponding] to at least one copy of a mRNA instability sequence.

5. (Once amended) A stably transfected cell line comprising the [a] reporter gene DNA expression system of [according to] claim 4.

6. (Once amended) An assay system for the identification of compounds which destabilize mRNA comprising the [a] reporter gene DNA expression system of [as defined in] claim 4, and a control DNA expression system which comprises a gene coding for expression of the protein having the detectable signal, wherein the gene comprises DNA coding for the amino acid sequence of the protein operably linked to [together with associated] 5′ and 3′ UTR sequences comprising appropriate expression control elements but lacking any functional mRNA instability sequence.

7. (Twice amended) An assay system comprising a stably transfected cell line according to claim 5, and a stably transfected cell line comprising a control DNA expression system which comprises a gene coding for expression of the protein having the detectable signal, wherein the gene comprises DNA coding for the amino acid sequence of the protein operably linked to [together with associated] 5′ and 3′ UTR sequences comprising appropriate expression control elements but lacking any functional mRNA instability sequence.

8. (Once amended) A stably transfected cell line comprising the [a] reporter gene DNA expression system of [according to] claim 4 and a control gene DNA expression system, said control gene DNA expression system comprising a gene coding for expression of a protein having a detectable signal which is different than the protein of the reporter gene DNA expression system and wherein said control gene DNA expression system comprises DNA coding for the amino acid sequence of the protein operably linked to [together with associated] 5′ and 3′ UTR sequences comprising appropriate expression control elements but lacking any functional mRNA instability sequence.

11. (Once amended) A method of treating or preventing [Use of a compound according to claim 10 for the prophylaxis or treatment of] a disease or medical condition in a subject, wherein the disease or medical condition is associated with [which involves] inappropriate mRNA stabilisation and/or accumulation and undesirable protein expression, comprising administering to the subject the compound of claim 10.

12. (Once amended) A compound which destabilizes mRNA identified by the use of the [a] DNA expression system of [according to] claim 4.

13. (Once amended) A compound which destabilizes mRNA identified by the [a] cell line of [according to] claim 5 or 8.

14. (Once amended) A compound[s] which destabilizes mRNA identified by the [an] assay system of [according to] claim 6, 7 or 9.